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## Adrenergic Fibres to the Brain and Spinal Cord Vessels in the Dog

by

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### INTRODUCTION

The essentially determining role of the adrenergic innervation of the blood vessels for the regulation of the blood flow has been well accepted. The blood flow in the central nervous system is determined by two opposing sets of forces : the effective perfusion<sup>10)</sup> pressure and cerebral vascular resistance. The relation of arterial blood pressure to cerebral flow is also determined by the level of the blood pressure itself. A lowering of the mean arterial blood pressure to a level of about 60 to 70 mmHg by means of high spinal anesthesia, paralyzing most of the sympathetic vasoconstrictor nerves, has no effect on cerebral blood flow, which remains constant<sup>12)</sup>. This indicates the compensatory lowering of the vascular resistance in brain. Similarly, an elevation of blood pressure is without effect on blood flow of the brain due to a secondary increase in the vascular resistance<sup>18)</sup>. Although several extravascular factors such as intracranial pressure<sup>11)</sup> and the viscosity of the blood<sup>17)</sup> contribute to the cerebral vascular resistance, the most important component of cerebral vascular resistance is the diameter of the cerebral blood vessels. Though the cerebral vessels are supplied also by adrenergic nerve fibers, the bilateral blocking of the stellate ganglia fails to produce any change in cerebral vascular resistance or blood flow, contrary to what might be expected if these nerves were normally contributing to the maintenance of cerebral vascular tone.

The introduction of the histochemical demonstration of the endogenous noradrenaline by FALCK<sup>15)16)</sup> and HILLARP made the distribution of the adrenergic nerve fibers in the walls of the blood vessels visible microscopically. FALCK<sup>2)</sup> described the presence of the adrenergic nerve fibers in some of the arteries in the vicinity of the spinal cord. In the present investigations this fluorescent technique modified by FUJIWARA<sup>8)</sup> et al. was employed for the distribution study of the adrenergic nerve fibers in the blood vessels of the brain and spinal cord of the dog.

### MATERIAL AND METHODS

Forty adult healthy mongrel dogs of various sex and weighing 5 to 15 kg were used. All animals were anesthetized with intravenous nembutal sodium in the dose of 30 mg/kg. Small pieces of tissue were taken from the brain and spinal cord and were frozen in isopentane, freeze-dried, treated with formaldehyde and sectioned for fluorescence microscopy. In order to increase the amine contents and thereby to intensify the fluorescence

of the adrenergic fibers, certain animals were treated with nialamide 50 mg/kg intraperitoneally, and 24 hours later, 200  $\mu$ g/kg of noradrenaline in 20 ml of the physiological saline was injected intravenously during 5 minutes. The animals of another group were treated with the intraperitoneal injection of 0.5 mg/kg of reserpine twice a day at a time interval of 12 hours for succeeding three days, and 24 hours after the last injection the animals were killed for the fluorescent histochemical procedures. The borohydride reduction<sup>3)</sup> test was sometimes undertaken to differentiate the specific fluorescence from high autofluorescence in the tissues.

The bilateral superior cervical, the bilateral stellate, the bilateral thoracic (Th-4 to Th-12) and the bilateral lumbar sympathectomies (L-2 to L-6) were performed on the respective 5 animals. All of these operative procedures were aseptically performed. Seven days after the surgical operation the animals were sacrificed by bleeding.

The vessels studied were the internal carotid artery, the vertebral artery, the circle of Willis, the basilar artery, the middle cerebral artery and its branches, the anterior and posterior spinal arteries at the level of the 2nd and 6th cervical segments, the 2nd, 7th and 11th thoracic segments and the 2nd and 5th lumbar segments of the spinal cord.

## RESULTS

The treatment of the freeze-dried tissue specimens with formaldehyde for one hour demonstrated the green or yellowish green fluorescent fibers in certain structures of the arteries. The fibers showed the varicose structures in their course. Since this fluorescence was confirmed to represent the endogenous noradrenaline by the quenching of the fluorescence with the borohydride treatment and by the disappearance of the fluorescence in response to the sympathetic denervation of the tissues, the fluorescent fibers were referred to the adrenergic nerves.

### I. Distribution of the adrenergic nerves

The transverse or longitudinal section of the internal carotid and vertebral arteries from the intact dog did not significantly exhibit the specifically fluorescent presence of the adrenergic nerve fibers in their walls. However, the previous treatment of the animals with nialamide or noradrenaline enabled the visualisation of the fibers by intensifying the fluorescence. The description of the adrenergic nerve fibers in the internal carotid and vertebral arteries below was in the dog treated with either agent. No significant difference in the fluorescent intensification between both treatments was found.

#### Internal carotid artery :

As shown in Fig. 1, the fluorescent fibers in the internal carotid artery 1 to 2 mm in diameter were abundantly found in the tunica adventitia at the sites of the external elastic membrane. None of the fibers invaded into the media. The multiplicity of the fluorescent fibers in the course exhibited the bundle-like and net structures. The fluorescences of the internal elastic membrane and elastic fibers in the tunica media proved to be non-specific.

#### Vertebral artery :

Much less distribution of the fluorescent fibers was found in the vertebral artery than in the internal carotid artery. Moreover, the relatively large-sized fluorescent fibers were

found sporadically at the external elastic membrane immediately adjacent to the smooth muscles of the media (Fig. 2). The internal and external elastic membranes as well as some of the elastic fibers of the media exhibited the nonspecific fluorescence.

#### Basilar artery :

The specific fluorescent nerve fibers in the basilar artery about  $300\mu$  in diameter are shown in Fig. 3. The bead-like structure of the fluorescent fibers varying considerably in diameter was found in the adventitial layer immediately adjacent to the smooth muscles of the media. None of the fibers invaded to the muscle layer.

#### Circle of Willis :

The similar bead-like structure of the specific fluorescent fibers as that of the basilar artery was observed in the circle artery of Willis about  $400\mu$  in diameter. The internal elastic membrane exhibited a non-specific fluorescence. (Fig. 4)

#### Middle cerebral artery :

Owing to the loose consistency of the external layers, the fluorescent fibers with varicose structures which show an enlarged distribution is the adventitial layers of the middle cerebral artery about  $200\mu$  in diameter. (Fig. 5)

#### Branch of the middle cerebral artery :

The small branch of the middle cerebral artery about  $30\mu$  in diameter showed the thin internal elastic membrane and the loss of elastic fibers in the loose connective tissue of the tunica adventitia. Only a few specific fluorescent fibers could be found in the adventitia of the vessels and they were sometimes traced longitudinally along the artery. A pair of the fluorescent fiber was found at the mutually opposite location across the artery. (Fig. 6)

#### Anterior spinal artery :

The specific fluorescent fibers in the cross sections of the anterior spinal artery at the levels of Th-11 and C-2 to L-5 showed the distribution pattern similar with that of the basilar or middle cerebral artery, as shown in Fig. 7.

#### Posterior spinal artery :

The posterior spinal artery at the levels of Th-7 and C-2 to L-5 showed the distribution of the fluorescent fibers in the adventitia immediately adjacent to the muscle layers of the media. The distribution pattern of the fluorescent fibers in the cross section indicates the longitudinal extension of the fibers along the artery. (Fig. 8)

In contrast to the fairly abundant presence of the specific fluorescent nerve fibers in the middle or small-sized arteries, the cerebral and spinal cord veins did not usually exhibit the specifically fluorescent fibers in the wall.

## II. Effects of the sympathetic ganglionectomy on the specific fluorescence of the arteries

The previous reserpinization of the animals resulted in the almost total disappearance of the specific fluorescence of the arteries without affecting the nonspecific fluorescence of the elastic membranes and fibers.

The bilateral superior cervical ganglionectomy induced total disappearance of the specific fluorescence of only the internal carotid artery, middle cerebral artery, branches of the middle cerebral artery, circle of Willis and basilar artery. (Fig. 9, 10, 11)

**Table 1** The results of various bilateral sympathectomies on the vessels 7 days following operative procedure. The sign (+) shows the existence of the adrenergic fibres and (-) indicates disappearance of the adrenergic fibers.

		Control	Sympathectomy			
			Superior cervical ganglion	Stellate ganglion	Thoracic ganglion Th <sub>4</sub> -Th <sub>12</sub>	Lumbar ganglion L <sub>2</sub> -L <sub>6</sub>
Vertebral artery		+	+	-	+	+
Internal carotid artery		+	-	+	+	+
Middle cerebral artery		+	-	+	+	+
Circle of Willis		+	-	+	+	+
Basilar artery		+	-	+	+	+
Spinal	C <sub>2</sub>	+	+	-	+	+
	C <sub>6</sub>	+	+	-	+	+
	Th <sub>2</sub>	+	+	-	+	+
Cord	Th <sub>7</sub>	+	+	+	-	+
	Th <sub>11</sub>	+	+	+	-	+
Segment	L <sub>2</sub>	+	+	+	-	+
	L <sub>5</sub>	+	+	+	+	-

The bilateral stellate ganglionectomy resulted only in total disappearance of the specific fluorescence in the vertebral artery and anterior and posterior artery at the spinal levels from C-2 to Th-2. (Fig. 12)

The bilateral removal of the thoracic ganglion from Th-4 to Th-12 induced total disappearance of the adrenergic fluorescence in the anterior and posterior spinal arteries at the spinal levels from Th-7 to L-2.

The bilateral lumbar sympathectomy from L-1 to L-6 produced total disappearance of the fluorescence in the anterior and posterior spinal arteries at the spinal level of L-5.

The results of the sympathetic ganglionectomy were shown Tab. 1.

## DISCUSSION

The adrenergic innervation of the arteries supplying the brain and spinal cord in the dog was confirmed by the histochemical demonstration of noradrenaline fluorescence. The intensity of the fluorescence seemed to be reflected by the concentration of the endogenous noradrenaline<sup>13,15</sup>). In this respect, the internal carotid and vertebral arteries exhibited no or very faint fluorescent fibers. This does not mean the absence of the adrenergic innervation of the arteries, since the previous treatment of the animal with nialamide or noradrenaline itself produced a significant visualisation of the fluorescent fibers in the tunica adventitia immediately adjacent to the smooth muscles of the media. The physiological significance of the relatively little amount of the endogenous noradrenaline in the adrenergic nerve fibers innervating the arteries of large caliber remains unknown. On the other hand, the cerebral and spinal arteries of medium or small caliber exhibited the abundant amount of the noradrenaline fluorescence in the innervating adrenergic nerve fibers. Similarly the abundant amount of the noradrenaline fluorescence in the adrenergic

nerve fibers of the peripheral arteries was shown by TSUNEKAWA et al.<sup>23)24)</sup>

The surgical removal of the bilateral superior cervical ganglia resulted in the total disappearance of the specific fluorescence in the internal carotid, middle cerebral, circle of Willis and basilar arteries at 7 days thereafter. On the other hand, the same procedure of the bilateral stellate ganglia did not affect the specific fluorescence in these intracranial arteries. The pharmacological blocking of the stellate ganglia has been recommended as one of the effective treatment for the vasospastic disorders of the brain<sup>1)14)</sup>. However, there are numerous controversial evidences showing that this procedure does not affect the cerebral vascular resistance or blood flow<sup>9)19)20)21)22)</sup>. The operative procedure of stellatectomy did not induce total disappearance of the specific fluorescence of the intracranial vessels, because the stellatectomy is considered not to denervate but decentralize the most of sympathetic nerve fibers to intracranial vessels. Therefore, the pharmacological blocking of the stellate ganglion, if it is really effective in relieving vasospastic disorders of the brain, may derive from the interruption of some afferent impulse pathway through the stellate ganglia but not from the interruption of the efferent adrenergic impulse. However, no such possibility has been demonstrated physiologically or histologically.

The abundant amount of the noradrenaline fluorescence in the adrenergic nerve fibers innervating the intracranial arteries allows the assumption that the vertebral and spinal blood flow and vascular resistance are regulated by the sympathetic nervous system. The fact that the autoregulation of the cerebral circulation becomes ineffective, when mean blood pressure falls below 60 mmHg is rather indicative for the reflex nature of the regulation mechanism<sup>7)</sup>, which normally is maintained by the adrenergic innervation of the blood vessels.

Surgical procedure of sympathectomy has been granted as one of the treatment for the vascular disorder of the brain. However little concern have been paid to its application for spinal vascular insufficiency. The total disappearance of the specific fluorescence in the spinal arteries at the levels from Th-7 to L-2 after resection of the bilateral thoracic sympathetic chain supports the beneficial effect of the spinal circulation by either block or operative resection of the paravertebral sympathetic chain.

IKEDA<sup>10)</sup> reported that the circulation of the lumbar segment of the spinal cord is affected not solely by the lumbar sympathetic ganglion, but also by the sympathetic ganglion of higher level.

TSUNEKAWA<sup>25)</sup> reported several cases of "non specific" encephalomyelitis with sensorimotor disturbances of the lower extremities. Their clinical pictures were improved remarkably following either block or resection of the upper thoracic sympathetic chain. The mechanism of the beneficial effect is not entirely clear, but possibility of the improvement of spinal cord circulation as a result of the sympathetic denervation was confirmed by these experiments.

#### SUMMARY

1) Adrenergic innervation of vessels in the brain and spinal cord was investigated histochemically in dogs.

2) In order to demonstrate the adrenergic nerve fibers the fluorescence microscopical technique was employed.

3) The adrenergic nerve fibers in the intracranial and spinal cord arteries was observed in the adventitial layer immediately adjacent to the smooth muscles of the media. None of the fibers invaded into the media.

4) The adrenergic nerve fibers was found in the relatively small-sized arteries of the brain and spinal cord.

5) The cerebral and spinal cord veins did not usually exhibit the specifically fluorescent fibers in the wall.

6) The influence of various sympathetic denervation upon the adrenergic fibers of the vessels distributing central nervous system was studied.

7) The postganglionic adrenergic innervation of the intracranial vessels is mainly regulated by the superior cervical ganglion.

8) The operative procedure of stellate ganglionectomy did not induced total disappearance of the specific fluorescence of the intracranial vessels.

9) The stellate ganglionectomy is considered not to denervate but decentralize the most of sympathetic nerve fibers to the intracranial vessels.

10) The specific fluorescence of the adrenergic nerve fibers in the vessels of the spinal cord at the C-2 to Th-2 segments were disappeared by the bilateral stellate ganglionectomy, similarly that at the Th-7 to L-2 segments by the thoracic (Th-4 to Th-12) ganglionectomy and that at the L-5 segments by the lumbar ganglionectomy respectively.

11) Possibility of the improvement of spinal cord circulation as a result of either blocking or removal of the thoracic sympathetic ganglions was confirmed by these experiments.

#### ACKNOWLEDGEMENT

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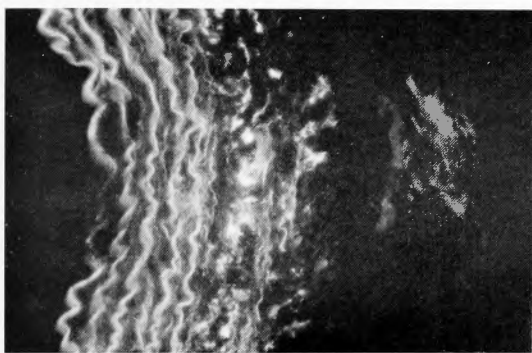
The abstract of this paper was presented before the 7th Annual Meeting of Japan College of Angiology, Tokyo, Oct. 16th 1966, Symposium of international society for neurovegetative research on neurohormones and neurohumors, Amsterdam, July 24th 1967 and the 20th Annual Meeting of Japan Society of Neurovegetative Research, Fukuoka, Oct. 28th 1967.

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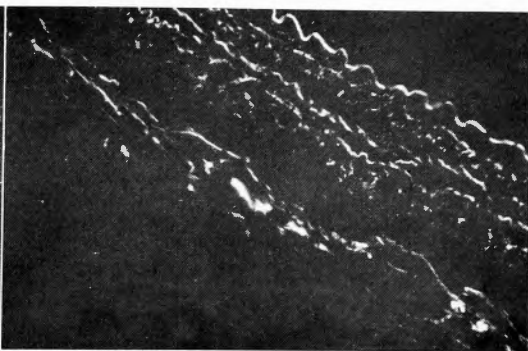
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**Fig. 1** Internal carotid artery, cross section. The fluorescent fibers in the internal carotid artery 1 to 2 mm in diameter were abundantly found in the tunica adventitia at the sites of the external elastic membrane.  $\times 128$ .



**Fig. 2** Vertebral artery, cross section. Much less distribution of the fluorescent fibers was found in the vertebral artery than in the internal carotid artery.  $\times 128$ .



**Fig. 3** Basilar artery, cross section. The bead-like structure of the fluorescent fibers varying considerably in diameter was found in the adventitial layer immediately adjacent to the smooth muscles of the media.  $\times 128$ .



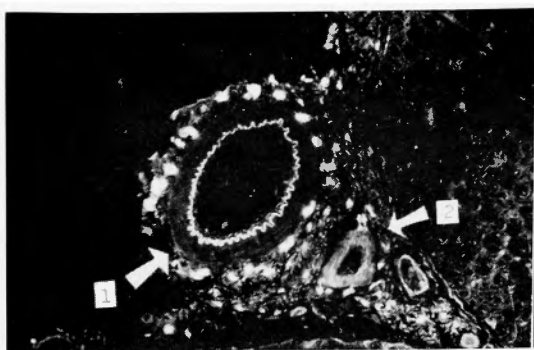
**Fig. 4** Circle of Willis, cross section. The bead-like structure of the specific fluorescent fibers was observed in the circle artery of Willis about  $400\mu$  in diameter.  $\times 128$ .



**Fig. 5** Middle cerebral artery, cross section. Owing to the loose consistency of the external layers, the fluorescent fibers with varicose structures which showed an enlarged distribution is the adventitial layers of the middle cerebral artery about  $200\mu$  in diameter.  $\times 128$ .



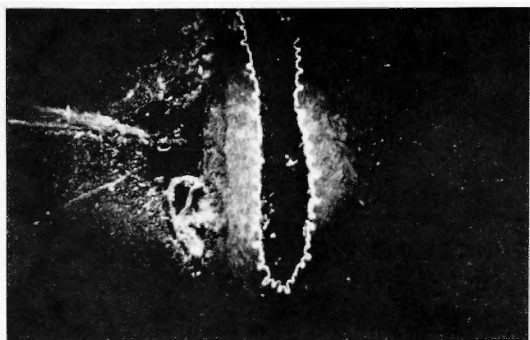
**Fig. 6** Branch of the middle cerebral artery, cross section. A pair of the fluorescent fibers were found at the mutually opposite location across the artery.  $\times 128$ .



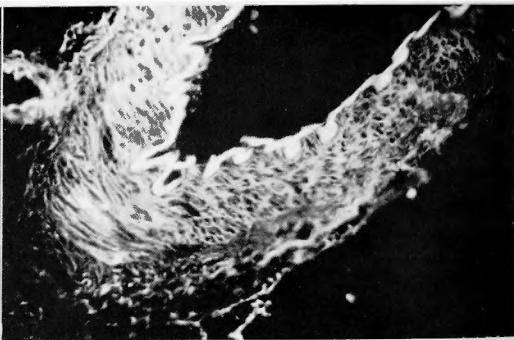
**Fig. 7** Anterior spinal artery, (Arrow. 1) cross section. The specific fluorescent fibers in the cross section of the anterior spinal artery at the levels of Th-11 and C-2 to L-5 showed the distribution pattern similar with that of the basilar or middle cerebral artery. Anterior sulcal artery (arrow 2), shows a few specific fluorescent in the adventitia around the vessel.  $\times 128$ .



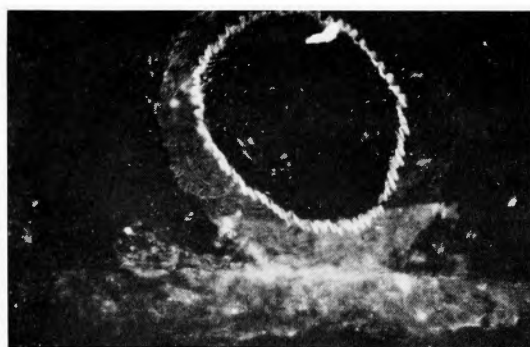
**Fig. 8** Posterior spinal artery, cross section. The posterior artery at the levels of Th-7 and C-2 to L-5 showed the distribution of the fluorescent fibers in the adventitia immediately adjacent to the muscle layers of the media. The distribution pattern of the extension of the fibers along the artery.  $\times 128$ .



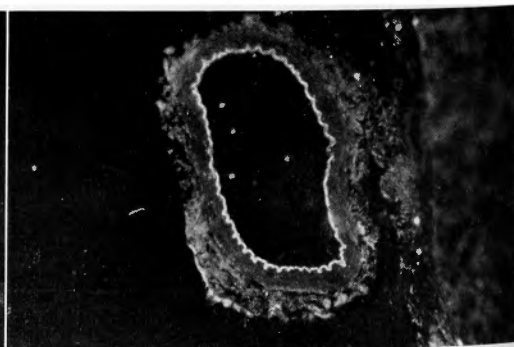
**Fig. 9** Middle cerebral artery, cross section, after bilateral superior cervical ganglionectomy 7 days. Total disappearance of the specific fluorescence can be seen.  $\times 128$ .



**Fig. 10** Circle of Willis, cross section, after bilateral superior cervical ganglionectomy 7 days. Total disappearance of the specific fluorescence can be seen.  $\times 320$ .



**Fig. 11** Basilar artery, cross section, 7 days after bilateral superior cervical ganglionectomy. Total disappearance of the specific fluorescence can be seen.  $\times 128$ .



**Fig. 12** Anterior spinal artery, cross section, at the level of Th-2, 7 days after bilateral stellate ganglionectomy. Total disappearance of the specific fluorescence can be seen.  $\times 128$ .

## 和 文 抄 録

犬における脳及び脊髄血管のアドレナリン  
作動性神経の分布に関する研究

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一般に、血管を支配する交感神経が血流調節において極めて重要な役割を演じていることは知られている。一方中枢神経系内血管の神経支配については諸家によりその特異性が論ぜられてきておりながらも尚形態学的にも生理学的にも未解決の多くの問題が残されている。

本研究の目的は組織化学的方法により脳及び脊髄の血管のアドレナリン作動性神経の神経支配の様相を知りこれら諸血管の血流調節の機構の一端を解明しようとするものであり、更に臨床的見地から交感神経遮断又は切除等外科的手技の適用を意図したものである。

Falck, 及び Hillarp により開発された endogenous noradrenaline の組織学的証明は血管壁におけるアドレナリン作動性神経繊維の分布の顕微鏡観察を可能にしたが、本研究では藤原等により改良された組織化学的蛍光法を用い犬の脳及び脊髄血管のアドレナリン作動性神経の分布について検討した。

本法では検索に必要な組織は採取後直ちに isopentane dry ice によつて凍結、その後7日間-35℃にて凍結乾燥を行ない、終了後80℃1時間 formaldehyde gas を作用する。この操作の間 noradrenaline は拡散することなく formaldehyde と縮合して強い蛍光性の dihydroisoquinoline となるのでこれを 蛍光顕微鏡により観察するものである。

尚血管のアドレナリン作動性神経における noradrenaline の生理学的意義を求めその消長を検討する目的から実験動物に予め次の様な処置を行なつた。1) Monoamine oxidase (MAO) Inhibitor 注入後 Noradrenaline 注入、2) Reserpine 投与、3) 交感神経切除。

無菌的に上頸部交感神経節切除、星状神経切除、胸部交感神経切除及び腰部交感神経切除を行ない術後7

日目の脳及び脊髄の種々な場所の血管のアドレナリン作動性神経の消長について検討した。

以上の実験を40頭の成犬を用いて行ない次の結論を得た。

1) 頭蓋内及び脊髄の動脈を支配するアドレナリン作動性神経は血管の中膜と外膜の境界部に存在し中膜内への侵入は認めない。

2) 中枢神経系内動脈におけるアドレナリン作動性神経支配を比較的細い血管にも認めた。

3) 脳及び脊髄の静脈系ではアドレナリン作動性神経の特異蛍光を認めず、交感神経支配があるとしても極めて微弱なものと考えられる。

4) 頭蓋内血管の節後性交感神経支配は主として上頸交感神経により行なわれている。

5) 星状神経切除では頭蓋内血管に分布する特異蛍光の消失を認めない。

6) 4)及び5)の結果より星状神経切除は頭蓋内血管に分布する大部分の交感神経繊維に対しdenervationではなくdecentralizationとしての意義があるとおもわれる。

7) 脊髄血管 C<sub>2</sub>-Th<sub>2</sub> に分布するアドレナリン作動性神経繊維の特異蛍光は両側星状神経切除により消失する。同様に Th<sub>7</sub>-L<sub>2</sub> は胸部交感神経切除 Th<sub>4</sub>-Th<sub>12</sub> により、L<sub>5</sub> は腰部交感神経切除により各々消失する。

8) 7)の結果より胸部交感神経切除又はブロックによる脊髄血行改善の可能性が示される。

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